29. Use according to any of Claims 25 to 28 for combating toxicity in an individual who has one of more clinical symptoms of toxicity caused by the antifolate compound.

30. Use according to Claim 29 wherein the clinical symptom of toxicity caused by the antifolate compound is selected from anaemia, anorexia, asthenia, dehydration, diarrhoea, fatigue, fever, hepatotoxicity, hyperbilirubinaemia, leukopaenia, mucositis, myelosuppression, nausea, neutropaenia, rash, reversible transaminitis, stomatitis, thrombocytopaenia and vomiting.

31. Use according to any of Claims 25 to 30 for combating toxicity in an individual who is administered a folate pathway rescue agent.

32. Use according to Claim 31 wherein the individual is administered the folate pathway rescue agent prior to the enzyme that has carboxypeptidase G activity.

33. Use according to Claim 31 wherein the individual is administered the folate pathway rescue agent after the enzyme that has carboxypeptidase G activity.

34. Use according to Claim 31 wherein the individual is administered the folate pathway rescue agent and the enzyme that has carboxypeptidase G activity substantially simultaneously.

35. Use of a folate pathway rescue agent in the preparation of a medicament for combating toxicity caused by an antifolate compound of Formula I as defined in Claim 1 or Claim 2 in an individual who is administered an enzyme that has carboxypeptidase G activity.

36. Use of an enzyme that has carboxypeptidase G activity and a folate pathway rescue agent in the preparation of a medicament for combating toxicity caused by an antifolate compound of Formula I as defined in Claim 1 or Claim 2.

37. Use according to any of Claims 31 to 36 wherein the antifolate compound is an inhibitor of DHFR or GARFT, and the folate pathway rescue agent is leucovorin.

38. Use according to Claim 37 wherein the antifolate compound is LY309887, AG2034, or AG2037.

39. Use according to any of Claims 31 to 36 wherein the antifolate compound of Formula I is an inhibitor of TS, and the folate pathway rescue agent is thymidine.

40. Use according to Claim 39 wherein the antifolate compound of Formula I is Tomudex.

41. Use according to any of Claims 25 to 40 wherein the enzyme that has carboxypeptidase G activity is at a dose of about 50 Units per kg body weight.

42. Use according to any of Claims 25 to 41 for combating toxicity caused by an antifolate compound of Formula I in an individual who is being treated for a disease selected from cancer, RA, MS, psoriasis, extrauterine pregnancy and graft vs. host disease by administration of the antifolate compound.

43. Use of an antifolate compound of Formula I as defined in Claim 1 or Claim 2 in the preparation of a medicament for treating a condition selected from cancer, RA, MS, psoriasis, extrauterine pregnancy and graft vs. host disease in an individual who is subsequently administered an enzyme that has carboxypeptidase G activity.

44. Use of an enzyme that has carboxypeptidase G activity in the preparation of a medicament for complementing the therapy of a disease selected from cancer, RA, MS, psoriasis, extrauterine pregnancy and graft vs. host disease that is being treated by administration of an antifolate compound of Formula I, wherein the medicament is for combating toxicity caused by the antifolate compound of Formula I.

45. Use according to any of Claims 42 to 44 wherein the antifolate compound of Formula I and the cancer to be treated are as defined in any of Claims 21-24.

46. A therapeutic system comprising an antifolate compound of Formula I as defined above in Claim 1 or 2, and an enzyme that has carboxypeptidase G activity.

47. A therapeutic system according to Claim 46 further comprising a folate pathway rescue agent.

48. An *ex vivo* method of cleaving a terminal L-glutamate moiety from a compound of Formula I as defined in Claim 1 or Claim 2, the method comprising contacting the compound with an enzyme that has carboxypeptidase G activity.

49. A method of determining the rate and/or extent of cleavage of a compound of Formula I as defined in Claim 1 or Claim 2 by an enzyme that has carboxypeptidase G activity, the method comprising:

providing the compound of Formula I,

contacting the compound of Formula I with an enzyme that has carboxypeptidase G activity under conditions such that cleavage of the compound can occur, and

monitoring the rate and/or extent of cleavage of the compound of Formula I over time.

50. A method according to Claim 49 wherein the monitoring step comprises monitoring the amount and/or concentration of the compound of Formula I.

51. A method according to Claim 49 or 50 wherein the monitoring step comprises monitoring the amount and/or concentration of one or more break-down products of the compound of Formula I.

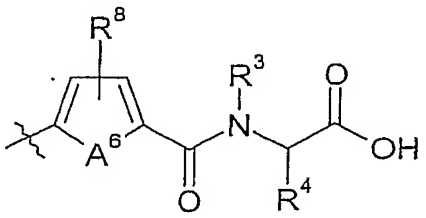
52. A method according to any of Claims 49 to 51 which is performed *ex vivo*.

53. A method according to any of Claims 49 to 51 which is performed *in vivo*.

54. A method according to Claim 53 further comprising determining whether an additional dose of the enzyme that has carboxypeptidase G activity is required in order reduce the amount of the compound of Formula I to a predetermined level.

55. A method according to Claim 53 or 54 further comprising contacting the compound of Formula I with an additional dose of the enzyme that has carboxypeptidase G activity under conditions such that cleavage of the compound can occur.

56. A method of cleaving a compound comprising a structural fragment of Formula VIII,



VIII

wherein

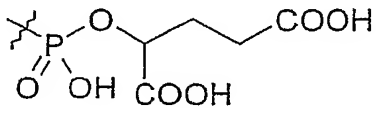
the wavy line indicates the point of attachment of the structural fragment;

A^6 represents O or S;

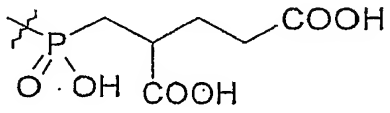
R^8 represents H or one or two substituents selected from halo, C_{1-4} alkyl and C_{1-4} alkoxy;

R^3 represents H or C_{1-4} alkyl;

R^4 represents $-CH_2C(R^{9a})(R^{9b})-D$;
R^{9a} and R^{9b} independently represent H or C_{1-4} alkyl, or R^{9a} and R^{9b} together represent $=C(H)R^{10}$;
R^{10} represents H or C_{1-4} alkyl;
D represents C(O)OH, tetrazol-5-yl, $(CH_2)_{0-1}$-NHR^{11}, or, when R^{9a} and R^{9b} together represent $=C(H)R^{10}$, then D may also represent H, or D represents a structural fragment of Formula IIIa or IIIb,



IIIa



IIIb ;

wherein the wavy lines indicate the point of attachment of the structural fragments;
R^{11} represents H or $C(O)R^{12}$;
R^{12} represents H or phenyl substituted by C(O)OH and optionally substituted by one or two further substituents selected from halo, C_{1-4} alkyl and C_{1-4} alkoxy; and

alkyl, alkenyl and alkynyl groups, as well as the alkyl part of alkoxy groups, may be substituted by one or more halo atoms;

or a pharmaceutically acceptable salt and/or solvate thereof,

the method comprising contacting the compound comprising the structural fragment of Formula VIII with an enzyme that has carboxypeptidase G activity.

57. A method according to Claim 56 that is performed *ex vivo*.

58. A method according to Claim 56 that is performed *in vivo*.

59. A method according to Claim 56 wherein the compound comprising the structural fragment of Formula VIII is an antifolate compound.

60. A method according to Claim 59 for combating toxicity caused by the antifolate compound in an individual who has been administered the said antifolate compound in the course of medical treatment, or otherwise, the method comprising administering to the individual an enzyme that has carboxypeptidase G activity.

61. Use of an enzyme that has carboxypeptidase G activity in the preparation of a medicament for combating toxicity caused by an antifolate compound of Formula VIII as defined in Claim 56.

62. A method according to any of Claims 1 to 24 or 48 to 60, or a use according to any of Claims 25 to 45 or 61, or a therapeutic system according to Claim 46 or 47, wherein the enzyme that has carboxypeptidase G activity is carboxypeptidase G_2, or a derivative thereof which has carboxypeptidase G activity.